REMARKS

The Amendments

Applicants have amended claim 11 to make it independent and to recite all of the limitations of its former base claim (claim 23), as suggested by the Examiner. Claims 12 and 13 depend from now independent claim 11 and have, thus, not been amended. The Examiner stated that these three claims would be allowable in independent form. Applicants respectfully request their allowance.

The Rejections Under 35 U.S.C. § 102

For prior art to anticipate a claim under § 102, it has to meet every element of the claimed invention. The case law is clear on the "all elements" requirements of an anticipatory reference. "An anticipation rejection requires showing that each limitation of a claim must be found in a single reference, practice or device". *In re Donohue* , 766 F. 2d 531,534 (Fed. Cir. 1985). All the elements must be found "within the four corners" of the prior art reference. *Advance Display Sys. Inc. v. Kent State Univ.*, 212 F. 3d 1272, 1283 (Fed. Cir. 2000). The exclusion or absence in the prior art reference of even one claim element is enough to negate anticipation by that reference. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984).

Shah does not disclose all the elements of the mutant kinases of claim 10 or 23. Hence, it cannot, as a matter of law, anticipate these claims.

First, as acknowledged by the Examiner, Shah's mutant protein tyrosine kinase, v-Src GST-XD4 (V323A, I338A), does not have at least one amino acid substitution in its ATP binding site compared to the naturally-occurring protein kinase. Yet, this element is

required by claims 10 (a) and 23 (a). Second, as acknowledged by the Examiner, Shah's mutant kinase does not bind compounds in its ATP binding site with a dissociation constant less than 10 μM. This element is required by claims 10 (b)(i) and 23 (b)(i). Finally, Shah does not teach a mutant of a naturally occurring second *serine/threonine* protein kinase. Shah refers to a mutant of a *tyrosine* kinase. Claim 23 requires a serine/threonine kinase. Given these undisputed facts, Shah does not anticipate either claim 10 or claim 23.

The claim elements that the Examiner concedes are missing from Shah are not makeweights or distinctions without differences. Each is critically important to the utility of the claimed mutants. The present invention relates to methods for designing inhibitors of kinases using ATP-binding site mutants of those kinases. The claimed mutants are intermediates in those methods. These methods are based upon the identification of residues *in the ATP binding pocket* of a first kinase that make close contact with an inhibitor and subsequently identifying and altering an amino acid in the ATP binding site of a second kinase to create the claimed mutant. Without the requisite mutations *in the ATP binding site*, the present invention could not be used to design inhibitory compounds that competitively bind at the ATP binding sites. See, e.g., p. 7, lines 18-20. Shah does not disclose an ATP binding site mutant.

Further, as taught in the detailed description of the invention, the ultimate inhibitor produced by the methods of this invention using the claimed intermediates must bind tightly to the kinase and significantly inhibit the ability of the kinase to hydrolyze ATP. See, e.g., p.9, line 8. Such inhibitory compounds could not be made without a dissociation constant for the compound of less than 10 μM. Preferably, the inhibitor will

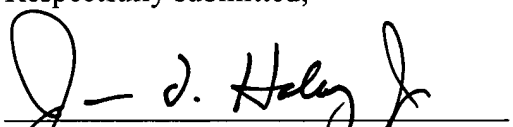
have greater binding affinity, with a dissociation constant of less than 100 nM. See, e.g., page 9, lines 10-11. This high level of binding affinity is integral to designing or selecting an inhibitor that binds to the kinase and thus is integral to the present invention.

Although Shah reports the dissociation constant of the mutant protein tyrosine kinase, v-Src GST-XD4 (V323A, I338A), as 10-fold lower than the dissociation constant of the naturally-occurring protein tyrosine kinase, v-Src GST-XD4, Shah does not require or disclose a minimal binding affinity (or maximal dissociation constant) for the compound to the mutated kinase. Yet, as explained above, without at least that level of binding the compound will not be an effective inhibitor. For example, a compound that binds to the claimed mutant at 1 M, could bind to the naturally occurring kinase at 0.1 M and satisfy the 10-fold lower requirement. However, this compound would not be appropriate as a kinase inhibitor. Shah does not disclose this requisite baseline level of binding.

Conclusion

For all of the foregoing reasons, applicants request that the Examiner reconsider all of the elements of the pending claims and Shah's failure to disclose those elements and withdraw the claim rejections and allow all of the claims of this application. If the Examiner believes that an interview would facilitate the resolution of any outstanding issues, he is invited to contact the undersigned.

Respectfully submitted,



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